REMARKS

Claims 1, 11-13, and 23-25, 35, and 36 have been amended, claims 53-64 have been added, and claims 2, 4, 6-10, 14, 16, 18-22, 26, 28, and 30-34 have been cancelled. Claims 3, 5, 15, 17, 27, 29, and 37-52 were previously cancelled. Upon entry of this amendment, claims 1, 11-13, 23-25, 35, 36, and 53-64 will be pending.

More specifically, claim 1 has been amended to recite a bone condition associated with breakdown of bone tissue or bone loss. Support for this amendment can be found, e.g., at paragraph [0006] of the specification (paragraph numbers refer to the specification as published under U.S. Patent Publication No. 2006/0116318). Claims 1, 13, and 25 have been amended to specify an effective amount of a peptide comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 1, 2, or 3. Support for this amendment can be found, e.g., in original claim 7 and at paragraph [0025] of the specification. Claim 25 has also been amended to replace modulating with inhibiting to promote clarity. Support for this amendment can be found, e.g., at paragraph [0058] in the specification. Support for amended claims 11, 12, 23, 24, 35, and 36 can be found, e.g., at paragraph [0026]. Support for new claims 53-61 can be found, e.g., in original claims 2 and 3 and at paragraph [0025]. Support for new claims 62-64 can be found, e.g., at paragraph [007] to paragraph [0018]. No new matter is added.

The claim amendments made herein have been made solely to expedite prosecution of the instant application and should not be construed as an acquiescence to any of the Examiner's rejections.

35 U.S.C. § 112, First Paragraph

Written Description

The Office rejected claims 1, 2, 4, 6-14, 16, 18-26, 28, and 30-36 under 35 U.S.C § 112, first paragraph, for allegedly failing to meet the written description requirement.

The Office alleged that "[a]pplicants arguments filed 12/27/2006 have been fully considered but they are not persuasive" (see the Office Action mailed March 20, 2007 (the "Office Action") at page 2, line 3). In upholding the rejection, the Office asserted that under 35

U.S.C. §112, first paragraph, it is critical that the "specification discloses a representative number of species to demonstrate that Applicants was in possession of the entire genus at the time the application was filed." The Office stated that "there is no *per se* rule regarding a "representative number"" and that even though the courts have ruled that under some circumstances a single species is sufficient to describe a broad genus, the determination is "case- and fact-dependent and is related to the predictability of the art." In the case of the instant application, the Office considered the breadth and composition of the genus, the extent to which the distinguishing identifying characteristics of the genus have been disclosed, and the predictability in the art. With respect to the breadth and composition of the genus, the Office alleged that "[t]he claimed genus is exceptionally broad with respect to structure however the genus must also possess as distinguishing functional characteristic, the ability to promote osteoblast proliferation, which narrows the scope of the genus" (see Office Action at page 3).

In response, applicants have removed "analogs" and "fragments of SEQ ID NO:1, 2, or 3" from claims 1, 13, and 25. Applicants have also amended claims 1, 13, and 25 to recite an amino acid sequence that is at least 90% (rather than 60%) identical to SEQ ID NO:1, 2, or 3.

Applicants respectfully submit that the specification discloses **three** distinct preptin peptides and the areas of variability between these peptides (e.g., R_1 to R_9 in formula (I)), as shown at paragraphs [007] to [018] of the application. As amended, claims 1, 13, and 25 include peptides that are at least 90% identical to either of these three distinct species. Applicants respectfully submit that methods for synthesizing peptides are routine in the art. The specification also discloses the distinguishing functional characteristic of these peptides (i.e., the ability to promote osteoblast proliferation), and an assay for measuring this activity. Thus, applicants respectfully submit that one of skill in the art could, without undue experimentation and inventive skill, easily synthesize any peptide that is at least 90% identical to SEQ ID NO:1, 2, or 3 and assay the activity of the peptide. Applicants respectfully submit, therefore that the specification discloses a representative number of species to demonstrate that applicant was in possession of the entire genus at the time the application was filed, and is adequate to meet the written description requirement for independent claims 1, 13, and 25.

With respect to the extent to which the distinguishing identifying characteristics of the genus have been disclosed, the Office asserted that

> [t]he complete structures of the 512 sequences represented by formula I have been disclosed, including SEQ ID NOs:1, 2, and 3. ... A correlation between the structure of these species and their function has not been presented, rendering it difficult for the skilled artisan to predict in the absence of experimentation, which of the 512 sequences would possess this functional property (see Office Action at page 4)

Applicants have disclosed three different peptides and have provided an alignment of the their sequences to show conserved regions. Given this information, one skilled in the art could easily obtain any species and assay its function using the *in vitro* assay described in the specification. Furthermore, one of skill in the art would reasonably understand that this *in vitro* test could be performed, for example, in a 96-well plate, thus allowing multiple assays to be easily performed simultaneously.

The Office's assertions regarding fragments, preptin analogs, and peptides with at least 60% homology to SEQ ID NOs:1, 2, or 3 are moot in light of the current amendments.

Applicants respectfully submit that, taken together, the embodiments disclosed, the functional limitation, and the assay provided to determine which peptides posses the distinguishing functional characteristic of the genus, are sufficient to fully describe the entire genus.

Applicants also respectfully submit that the above remarks also apply to newly added claims 62, 63, and 64, which refer to peptides comprising the amino acid sequence of formula (I).

In addition, the Office asserted that;

> Claims 1, 2, 4, and 6-12 fail to meet the written description requirement for the genus bone condition. The specification defines a bone condition as any disease wherein mediation of osteoblast or osteoclast activity is involved such as osteoporosis, osteopenia and bone defects. Is there any evidence in the prior art for a class of bone diseases that can be treated by targeting this underlying feature? The specification fails to describe the distinguishing characteristics of the entire genus. What patient population should be targeted? What are the symptoms of the diseases and methods of diagnosis? Bone defects in particular is broad and undefined. How is the skilled artisan to recognize which bone defects are related to osteoblast or osteoclast activity and which ones are not? The claims are not supported for the genus bone condition (Office Action at page 7, lines 3 to 12).

Based on the disclosure of the present application, applicants submit that one of skill in the art would clearly recognize that patients suffering from breakdown of bone tissue or bone loss could benefit from treatment with an agent that increases osteoblast activity. The population that should be targeted and the symptoms of the disease and methods of diagnosis would be apparent to one of skill in the art. Nevertheless, to promote clarity and facilitate prosecution applicants have amended claim 1 to read "[a] method for treating a bone condition associated with breakdown of bone tissue or bone loss, ..."

In light of the above remarks and amendments, applicants respectfully submit that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Enablement

The Office rejected claims 1, 2, 4, 6-14, 16, 18-26, 28, and 30-36 under 35 U.S.C § 112, first paragraph, for allegedly failing to meet the enablement requirement.

The Office alleged that "[a]pplicants arguments filed 12/27/2006 regarding the rejection of the claims for failing to comply with the enablement requirement of 35 U.S.C. 112 have been fully considered but they are not persuasive." The Office also discusses the full set of Wands factors, including the state of the prior art and it's predictability or unpredictability, the relative skill of those in the art, the breadth of the claims, the amount of direction or guidance presented and the presence of working examples, and the quantity of experimentation necessary (see Office Action at pages 7 to 13).

With respect to the state of the prior art and its predictability or unpredictability, the Office asserted that "it is unclear how preptin, which acts to stimulate osteoblast proliferation, could treat a disease characterized by overactive osteoblasts" and present Paget's disease as an example of such a disease. The Office also discusses osteoporosis as "a bone conditions that may be treated or prevented by therapies that "act at least in part by preventing osteoblast apoptosis and/or stimulating osteoclast apoptosis." (Jilka et al, Med. Pediatr. Oncol, 2003, 41, 182-5; see also Manolagas, Endocrine Rev., 2000, 21, 115-37)" (see Office Action at pages 8 to 9).

Applicants respectfully submit that as amended, the Office's remarks with respect to Paget's disease are moot, as one of skill in the art would not reasonably understand Paget's disease to be associated with breakdown of bone tissue or bone loss.

As disclosed in the specification, preptin stimulated the proliferation of primary fetal rat osteoblasts and osteoblast-like cell lines, and neonatal calvarial organ culture *in vitro*, and these effects appear to be dependent upon p42/p44 MAP kinase phosphorylation. Preptin is also anti-apoptotic in primary osteoblasts. *In vivo*, preptin stimulates osteoblast proliferation and differentiation, which is shown to significantly increase bone area and mineralizing surface compared to the control in sexually mature male mice (see Table 1 at page 5, and Table 2 at page 6 in the application). Thus, preptin is anabolic to osetoblasts. Preptin does not appear to affect osteoclast development. Applicants respectfully submit, therefore, that one of skill in the art would reasonably understand the therapeutic value of preptin for the treatment of a bone condition associated with breakdown of bone or bone loss.

With respect to the breadth of the claims, the Office discusses the size of the genus prior to the amendments made herein. In light of the amendments, applicants respectfully submit that this rejection is moot.

With respect to the amount of direction or guidance presented and the presence of working examples, the Office alleged that "the specification provides only limited working examples. ... The specification fails to address any address many questions that could guide the skilled artisan" and discusses the structure-function relationship of preptin. In response, applicants respectfully submit that, as amended, the working examples are sufficient to enable the claimed genus.

The Office also asserted that "[t]he specification fails to enable the full scope of the methods ... How is the skilled artisan to recognize conditions that can be treated by the claimed method in the absence of guidance from the specification?" (see Office Action at page 11).

In response, applicants resubmit that one of skill in the art would clearly recognize that patients suffering from breakdown of bone tissue or bone loss could benefit from treatment with an agent that increases osteoblast activity. The Office also asserted that "drugs that inhibit osteoblast apoptosis and promote osteoclast apoptosis are known to treat apoptosis. ... Is it sufficient to target osteoblast apoptosis but not osteoclast apoptosis" (see Office Action at page

11). In response, applicants submit that the Office describes drugs that seem to function solely by modulating osteoblast and osteoclast apoptosis. These examples are not relevant to the instant application, however, as preptin not only inhibits osteoblast apoptosis, but also promotes osteoblast proliferation and differentiation. Again, the therapeutic potential of preptin, therefore, would be immediately clear to a skilled artisan.

With respect to claims 13, 14, 16, and 18-22, the Office alleged that "[t]he specification presents data suggesting that rat preptin can increase bone area and mineralizing surface of bone. ... Does an increase in bone area or mineralizing surface correlate with an increase in bone density?" (Office Action at page 11, lines 17 to 21).

Attempts have been made to standardize and decipher nomenclature in the field, see for example Parfitt *et al.* (Parfitt *et al.*, *Journal of Bone and Mineral Research*, 2: 595-610, 1987). "Bone area," "mineralizing surface," and "bone density" are art-recognized terms. "Bone density," also known as bone mineral density (BMD), refers to a measure of the mass of bone in relation to its volume and/or the volume of calcium and minerals within bone tissue. "Bone area" and "mineralizing surface" are art-recognized bone formation markers. Applicants respectfully submit that increases in bone area and/or mineralizing surface correlate with increasing or maintaining bone density.

With respect to claims 25, 26, 28 and 30-36, the Office asserted that "the specification supports the inhibition of osteoblast apoptosis only" (see Office Action at page 11). In response, applicants have amended independent claim 25 to recite "[a] method for stimulating osteoblast growth or inhibiting osteoblast apoptosis, ..." In view of this amendment, applicants submit that this rejection is moot.

The Office also asserted that "specification provides insufficient guidance on how to select for active preptin peptides and on how to treat all bone conditions, increase bone density and modulate osteoblast apoptosis within the scope of the claims" citing Genetech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1966) and Rasmusson v. Smithkline Beecham Corp., 75 USPQ2d 1297 (CA FC 2005) (see Office Action at page 12). The Office also alleged that "the skilled artisan would be burdened with undue experimentation in determining if one of the claimed preptin peptides, fragment, analogs or homologs would be effective at treating bone diseases ... The experimentation required represents years of inventive

effort and would amount to more of a fishing expedition than routine investigation" (see Office Action at pages 12 to 13).

Applicants submit that these assertions are moot in light of the above amendments and remarks.

In light of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the above rejections under 35 U.S.C. §112, first paragraph.

35 U.S.C. § 112, Second Paragraph

The Office rejected claims 2, **24**, and 26 for being allegedly indefinite. The Office asserted that "claims 2, **14** and 26 recites the limitation "the amino acid sequence of preptin" in claims 1,13 and 25, respectively. There is insufficient antecedent basis for this limitation in the claim (see Office Action at page 13, emphasis added).

The Office first rejected claims 2, 24, and 26. However, the Office then asserted that "[c]laims 2, 24, and 26 are rejected under 35 U.S.C. 112, ..." Applicants will respond to the rejection with respect to claims 2, 14, and 26. Applicants respectfully submit that, as amended, claims 2, 14, and 26 are cancelled, thus the rejection is moot.

In light of the above amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C §112, second paragraph.

Enclosed is a Petition for Extension of Time with the appropriate fee. Also enclosed is a Notice of Appeal with appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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